201-14330

NCIC HPV
Sent by: Mary-Beth Weaver

03/05/2003 02:22 PM

To: NCIC HPV, Jodi Burgess/DC/USEPA/US@EPA
cc:
cc:
Subject: Environmental Defense comments on Estragole (CAS 140-67-0)

Richard_Denison@environmentaldefense.org on 03/04/2003 02:47:42 PM

To: oppt.ncic@epamail.epa.gov, hpv.chemrtk@epamail.epa.gov, Rtk Chem/DC/USEPA/US@EPA, Karen Boswell/DC/USEPA/US@EPA, tadams@therobertsgroup.net
cc: lucierg@msn.com, kflorini@environmentaldefense.org, rdenison@environmentaldefense.org

Subject: Environmental Defense comments on Estragole (CAS 140-67-0)

(Submitted via Internet 3/4/03 to oppt.ncic@epa.gov, hpv.chemrtk@epa.gov, boswell.karen@epa.gov, chem.rtk@epa.gov, lucierg@msn.com and tadams@therobertsgroup.net)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for Estragole (CAS 140-67-0).

The test plan and robust summaries for estragole were prepared by the Flavor and Fragrance High Production Volume Consortium. In general the test plan was well written and informative concerning the use and biological properties of estragole. While we agree with most of the recommendations made by the sponsor, we are recommending that a combined reproduction/development study be conducted on estragole.

The sponsor proposes to use surrogate data from chemicals having similar chemical structures as estragole to fulfill some of the HPV endpoints; they are, in essence, proposing a category. Members of this category include estragole, methyleugenol, myristicin, safrole and anethole. Although it is a close call, we agree with the inclusion of methyleugenol, myristicin and safrole because they do have similar structures and metabolic pathways and they appear to have similar toxicological and biological properties. The same cannot be said of anethole. The side chain double bond in anethole is at a different location than in the other proposed members, and there is good evidence that this difference changes the metabolic pattern. Most notably, a key oxidation step occurring at the 1 position of the side chain appears critical for causing some of the toxic effects, including cancer, observed for the p-alkoxyallylbenzene derivatives, and would not be expect to be the same in anethole.

Since the only developmental toxicology study available in the robust summary is for anethole, we recommend that the sponsor conduct a developmental toxicity study on estragole. Also, since the reproductive study presented in the summaries is for a chemical mixture containing only small amounts of estragole, the sponsor should consider conducting a combined reproduction/development study on estragole.

We agree with the other recommendations made by the sponsor regarding the adequacy of the data for repeat dose, acute toxicity and genetic toxicity studies. We also note that methyleugenol was the subject of a major NTP study, which demonstrated that it is a hepatocarcinogen, and it is listed in the "Report on Carcinogens" as reasonably anticipated to be a human carcinogen. Therefore, EPA and the sponsor should consider estragole as a probable human carcinogen if methyleugenol data are to be used as a surrogate for estragole. The sponsor seems to argue in the test plan that

the NTP studies were flawed. Those arguments are not convincing, as they failed to acknowledge that methyleugenol was found to be a carcinogen at all doses tested, in both rats and mice, and that the cancers were consistent with known mechanisms of chemical carcinogenesis. The listing of methyleugenol in the report on carcinogens was unanimously approved in four separate and independent reviews.

Thank you for this opportunity to comment.

George Lucier, Ph.D.
Consulting Toxicologist, Environmental Defense

Richard Denison, Ph.D.
Senior Scientist